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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/814,620	TZIANABOS ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,17,18 and 98-102* is/are pending in the application.

4a) Of the above claim(s) *98-100 and 102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 17, 18 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/02/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on 05/26/2009 is acknowledged.

2. Claims 1-7, 17-18 and 98-102 are pending.

3. Claims 3, 98-100 and 102 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/19/2008

4. Claims 1-2, 4-7, 17-18 and 101 are currently under examination as they read on a method for treating urticaria comprising administering PSA1 to a subject.

5. Applicant's IDS document filed on 04/02/2009 is acknowledged. References must have authors and publication dates to be included on an IDS document.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 4-7, 17-18 and 101 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method for treating **an allergic condition other than asthma** in **a subject**, comprising: administering to **a subject** having **an allergic condition other than asthma an isolated polymer** in an effective amount to treat the allergic condition, wherein the polymer **comprises repeating units of a charge motif characteristic of B. fragilis polysaccharide A (PSA), the motif being a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxyl, phosphate, phosphonate, sulfate, and sulfonate** of claim 1; wherein the motif is a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of phosphate, phosphonate, sulfate, and sulfonate of claim 2; wherein the subject is **free of symptoms otherwise calling for treatment with the polymer** of claim 4; wherein the polymer is **a polysaccharide** of claim 5; wherein the polymer is **a bacterial capsular polysaccharide** of claim 6; wherein the polymer is PSA1 of claim 7; wherein the method further comprises administering to **the subject** an anti-allergy medicament selected from the group consisting of glucocorticoids, antihistamines, and anti-IgE antibodies of claim 17; wherein the administering comprises administering to **the subject** having **an allergic condition other than asthma** multiple doses of the **isolated polymer** to treat **the allergic condition** of claim18; and wherein the **allergic condition other than asthma is urticaria** of claim 101. The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation for the same reasons as set forth in the Office Action mailed on 12/23/2008.

Applicant's arguments filed on 05/26/2009 have been fully considered, but are not found persuasive.

Applicant argues:

"Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 Fed. Circ. 1988), and include (1) the breadth of the claims, (2) the nature of the invention, (3) the quantization of experimentation necessary, (4) the amount of direction or guidance presented, (5) the presence or absence of working examples, (6) the state of the prior art, (7) the relative skill of those in the art, and (8) the predictability of the art. Applicant will analyze the claimed invention according to the *Wands'* factors and show that the claimed invention was enabled.

(1) Breadth of the claims/(2) nature of the invention

The claimed invention pertains to a method for treating an allergic condition other than asthma or eczema by the administration of a polymer with a specific charge motif. Firstly, the specification provides a genus of well characterized polymers with a specific charge motif and shows that the charge motif has the claimed functionality, namely the ability to treat allergic conditions. Secondly, the methods of treatment are directed to allergic conditions, which is a single category disease that is well described in the art. Thus, the specification in combination with the art provides support for the breath of the claims. (3) the quantization of experimentation necessary / (4) the amount of direction or guidance presented.

The specification provides guidance, including working examples, on how to practice the methods of the claimed invention. The specification teaches how to treat an allergic condition by administering the polymers with the recited charge motif. In addition, the specification provides methods for evaluating the efficacy of the claimed treatment methods *(e.g.,* by measuring the suppression of the level of IgE antibodies).

(5) the presence or absence of working examples.

The specification provides working examples for the methods of the claimed invention. The specification teaches that polymers as diverse as peptides and polysaccharides show an immunomodulatory effect, as long as the polymers have the recited charge motif (See *e.g.,* Example 1, page 49 and Examples 6 and 7, pages 54-55). In addition, Examples 5 and 8 show that administration of the polymers with the recited charge motif results in a decrease in the level of IgE antibodies, which is all that is needed to show treatment of an allergic condition.

(6) the state of the prior art, (7) the relative skill of those in the art, and (8) the predictability of the art.

Allergic conditions are well described in the art. The art provides the pathophysiology and underlying biochemical mechanisms of allergic conditions *(i.e.,* the induction of a Th2 response by allergens resulting in the production of IgE and the subsequent activation of mast cells and basophilic cells, ultimately resulting in the toxic mediators that cause the allergic response) and treatment methods for allergic conditions *(e.g.,* glucocorticoids, antihistamines, beta-adrenergic agonists, anticholinergics, cytokines and anti-IgE antibodies). The art teaches that, because all allergic conditions operate through a similar underlying mechanism, treatment methods for allergic conditions often work on more than one allergic condition. Because the field of the treatment of allergic conditions is well established the predictability in the field is high.

Thus, based on the teachings in the specification and the state and predictability of the prior art, Applicant has met the burden of demonstrating that the claimed invention meets the enablement requirement as set forth *In re Wands'. According to the Examiner, the genus of compounds encompassed by the instant claim recitation is nearly limitless, so it is unlikely that the genus of compounds could be well characterized. Respectfully, Applicant disagrees with this assertion.*

Firstly, the size of genus of compounds has no relation to the characterization of these compounds. The specification provides that polymers as diverse as peptides and polysaccharides have a consistent immunomodulatory effect, as long as the polymers have the recited charge motif (See e.g., Example 1, page 49 and Examples 6 and 7, pages 54-55). Furthermore, the specification has incorporated by reference US 5,679,654, US 5,700,787 and WO 00/59515. These documents provide a detailed analysis of polymers, including polysaccharides, with specific charge motifs and their immunomodulatory effects. The teachings in these documents show that polymers with the motif recited in the instant application have a predictable and consistent immunomodulatory effect, while polymers with a slightly different charge motif do not have such an effect (See *e.g.,* WO 00/59515, pages 35-43). Applicant notes that the Examiner acknowledges that some compounds of the genus are well characterized. Respectfully, Applicant believes that that characterization is not limited to "some compounds of the genus" as the specification clearly characterizes all compounds of the genus, as demonstrated above.

Secondly, the class of compounds with the recited polysaccharide charge motif is not "nearly limitless". For instance, Mazmanian et al., (cited by the Examiner in the Office Action) discuss the characteristics of polysaccharides PSA and PSB, which are examples of the polymers used in the methods of the claimed invention, and state "these molecules have an unprecedented structure: each molecule has both positively and negatively charged motifs in each repeating unit. It is unusual for a bacterial polysaccharides to be shown to have any positive charges, most are either neutral or negatively charged. It was proposed that this unique structural feature might be crucial for the T-cell activating property of PSA. This idea was eventually shown to be correct for both PSA and PSB" (Top right column page 852). Thus, polymers with the recited charge motif itself, as found in nature, are relatively unusual. The class of polymers with these charge motifs, including natural polysaccharides, is well defined and not "nearly limitless"

Further, according to the Examiner, the genus of allergic diseases exhibits diverse etiologies and phenotypes and the Examiner reasons that a treatment for one allergic disease therefore will not be a treatment for all. Applicant respectfully disagrees with this statement. The pathophysiology and underlying biochemical mechanisms of allergic conditions, including allergic asthma, are well described and are the same for all allergic conditions. Allergic conditions are induced by a Th2 response to an allergen, characterized the production of Th2 cytokines such as IL4 and IL13, and resulting in the induction of IgE. In turn, IgE activates basophilic and mast cells resulting in the inflammatory and toxic mediators that cause the allergic reaction. While there may be minor variations in the mechanism of the various allergic disorders, the overall pathophysiology is the same. The art provides that anti-allergic therapies can be used for the treatment of more than one allergic disorder. For instance, an anti-IgE antibody (Omalizumab) has been used to treat a variety of allergic disorders, including uticaria, asthma and peanut anaphylaxis (See *e.g.,* Miller et al., Clinical and Molecular Allergy 2008, 6:4; provided herewith). Thus, a method of treatment that results in the lowering of the levels of IgE., such as the administration of an anti-IgE antibody, provides a method of treatment for multiple allergic condition. The specification provides working examples for the treatment of asthma with the polymers PSA1 and CP1, whereby the administration of the polymers results in the lowering of the levels of anti-allergen IgE antibodies. Because the lowering of IgE levels is a general method for the treatment of any allergic conditions, the specification enables the treatment of any allergic condition.

The Examiner argues that a treatment regimen that results in the lowering of allergen specific IgE levels is not an effective treatment method for the allergic condition (page 7). Respectfully, Applicant believes that this assertion is unreasonable as the art shows that the lowering of IgE levels is a method for the treatment of allergic disorders (See *e.g.,* Miller et al., Clinical and Molecular Allergy 2008, 6:4;

provided herewith). In addition, Applicant believes that the Examiner has not met her burden in establishing a *primafacie* rejection in this matter because the Examiner provides no support for the statement that lowering the levels of IgE is not a method for the treatment of allergic disorders.

The Examiner states that Mazmanian et al. do not teach or suggest that zwitterionic polymers may be used to treat any particular allergy, much less all allergies, or that zwitterionic polymers have any direct effect on IgE production. The Examiner continues by stating that she is confused as to why Applicant is implying that zwitterionic polymers work to lower IgE levels. Respectfully, Applicant does not understand the Examiner' s confusion. The specification *shows* that the administration of the zwitterionic polysaccharides PSA and CP1 results in the lowering the levels of allergen induced IgE (Examples 5 and 8). Thus, Applicant provides a direct showing of the suppression of IgE levels by the administration of polymers with the recited charge motif. This direct showing can not be refuted by the Examiner' s citation of a reference that, allegedly, is silent on the effects of IgE production. Furthermore, in contrast to the interpretation of the reference by the Examiner, Applicant believes that Mazmanian et al. support the claimed invention, at least because the reference teaches that correcting the Th2 bias by *B. fragilis* polysaccharides, which are examples of the polymers of the claimed invention, may lead to the suppression of the onset of allergic and asthmatic disorders.

The Examiner states on page 8 of the Office action that she "has *provided evidence* that the recited polymers are not predicted to work on all allergic diseases". Applicants respectfully disagree with the statement by the Examiner. Applicant believes that, at most, the Examiner has provided some general statements that zwitterionic polymers can affect the immune system in a variety of ways. However, the Examiner has not shown that the polymers of the claimed invention are not predicted to lower IgE levels and that that the lowering of IgE levels is not a method for treating allergic conditions. Respectfully, Applicant believes that the Examiner has not made out a *prima facie* case in this respect.

The Examiner referred to Kalka-Moll et al. to support the statement that different zwitterionic polymers have different cell stimulatory effects. Respectfully, Applicant maintains that the Examiner has misinterpreted the teachings of Kalka-Moll et al. Kalka-Moll et al. merely show that the immunomodulatory potency of the zwitterionic polysaccharides is dependent on the length of the polysaccharides. The teachings of Kalka-Moll et al. do not support the assertion that zwitterionic polymers having different structures stimulate cellular immunity differently as Kalka- Moll et al. do not teach that polysaccharides with the recited charge motifs have different immunomodulatory effects. Kalka-Moll et al. merely show that some polymers with the recited charge motif are more effective than others, which does not question the enablement of the claimed invention As stated in the MPEP (§2164.01) "The test of enablement is not whether any experimentation is necessary, but rather whether, if experimentation is necessary, it is undue." *In re Angstadt,* 537 F.2d 498,504.

According to the Examiner, "the term "comprising" is open language that opens the claimed polymers to include additional molecules wherein the methods are not the result of the charge motif of the polymers at all". Respectfully, Applicant maintains that the Examiner' s interpretation of claims reciting the connector "comprising" has no legal basis. Firstly, Applicant has shown that the recited charge motif conveys the claimed functionality and that removal of the charge motif results in the loss of the claimed functionality. Thus, the polymers do not need to include "additional molecules" to obtain the claimed functionality. Secondly, the Examiner's assertion seems to challenge the use of the connector "comprising" in claim language in general. If the Examiner' s argument were correct, no claim with the term "comprising" would be enabled because the claim could be interpreted to include additional components or steps that are required to obtain the claimed functionality.

The Examiner states on page 9 of the Office Action that she is confused as to why patients without infection, surgery and trauma, as recited in claim 4, are included in the methods of the claimed invention. Respectfully, Applicant has shown that the claimed invention is enabled for the any subject. The claimed invention, therefore, is also enabled for subjects without infection, surgery and trauma, as recited in claim 4

> Thus, based on a *Wands'* factor analysis, Applicant believes that Applicant has shown that claimed invention is enabled as no undue experimentation is required to practice the claimed invention. In addition, Applicant believes that the Examiner has not shown that the claimed invention does not meet the enablement requirements.

It is the Examiner's position that, contrary to Applicant's assertion the genus of all "polymers" that exhibit the "charge motif of B. fragilis polysaccharide A (PSA) the motif being a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxyl, phosphate, phosphonate, sulfate, and sulfonate" is not well-characterized at all. As the Examiner has stressed previously, the claims read on any molecule with that charge motif. Some compounds of this genus are well-characterized. However, the number of compounds which are characterized are not representative of the genus of compounds encompasssed. It is an undue burden to determine the genus of polymers encompassed by such a claim recitation, much less to make and use the genus in an allergy treatment method.

In addition, and also contrary to Applicant's assertion, the specification has not shown that a single polymer has the claimed functionality, much less the genus of polymers encompassed. The specifiation has not treated any allergic condition other than asthma with any polymer, nor has the specification treated more than one allergic condition other than asthma with any single polymer. Therefore, the specification has certainly not shown that every polymer can treat every allergic condition other than asthma.

Allergic conditions are not "a single category of disease" that may be treated by the same method, the Examiner provides a number of references that teach this fact. Kormelink et al. (PTO-892; Reference U) teaches that there is a subgroup of allergic diseases that displays common symptoms of allergies associated with IgE and have activated mast cells, but lack

elevated levels of total serum IgE and antigen specific IgE. In patients with non-IgE related allergic disorders, therapies that target IgE will not work (In particular, abstract). Kormelink et al. also teaches that this set of allergic disorders may be mediated by free immunoglobuilin light chains (In particular, abstract, whole document). Jyonouchi et al. (PTO-892; Reference V) teaches that non-IgE mediated food allergies primarily affect the gastrointestinal mucosa and display their own unique immune reactivity and cytokine production profile, which differs from that of IgE mediated food allergy and is typically only treated with an elimination diet. (In particular, abstract, pages 5-6, whole document). Greenberger et al. (PTO-892; Reference W) teaches that drug allergy is unpredictable and may be IgE mediated or non-IgE mediated (In particular, abstract). Bilo et al. (PTO-892; Reference X) teaches that Hymenoptera venom allergy may be IgE-mediated or non-IgE mediated (In particular, abstract, paragraph spanning page 1341-1342, first full paragraph on page 1345, whole document). Boguniewicz et al. (PTO-892; Page 2; Reference U) and Poonawalla et al. (PTO-892; Page 2; Reference V) teaches that urticaria, a skin rash, is caused by a number of autoimmune and other diseases, drugs, allergens, mechanical and thermal effects and sun damage (In particular Boguniewicz: Tables I and II, whole document; Poonawalla: Table I, whole document). Therefore, the terms "allergic condition," "urticaria" and "food allergy" are not single categories of disease mediated by IgE, contrary to Applicant's assertion. Therefore, the claimed method of treating all allergic conditions other than asthma is not enabled by the specification. In addition, the specification, which teaches treating asthma by the instant method is not enabling because Lemanske et al. (PTO-892; Page 2; Reference W) teaches that asthma is a complex disease having both genetic and environmental factors which, as of 2009, is not curable and whose treatment is complicated

and mostly aimed at just controlling symptoms (In particular, abstract, whole document). The animal model of asthma provided in the specification is not substantiating evidence in the form of animal tests which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746.

It is the Examiner's position that Tzianabos et al. teaches that in vitro and in vivo T cell activation using peptides with a zwitterionic charge motif depends on the number of repeating units. Zwitterionic peptides with less than 15 repeating untits were unable to stimulate T cells in vitro or in vivo. Therefore, the effects of the polymers encompassed, particularly with respect to peptides, are limited by size. Further, Kalka-Moll (IDS; 06/21/2004) teaches that polymer length affects the ability to stimulate cellular immunity, so zwitterionic polymers having different structures stimulate cellular immunity differently. Polymers of different lengths have different structures. Since all zwitterionic polymers of Kalka-Moll et al. are encompassed by the instant claim recitations, the reference shows that different zwitterionic polymers have different cell stimulatory effects and would in turn have different in vivo effects. The post-dated state of the art of Mazmanian et al. (PTO-892 mailed on 12/23/2008; Reference U) teaches that the recited zwitterionic polymers interact with T cells, B-cells and can direct the development of the immune-system toward a Th1 phenotype to suppress inflammation in general. However, the reference does not teach or suggest that zwitterionic polymers may be used to treat any particular allergy, much less all allergies or that zwitterionic polymers have any direct or indirect affect on IgE production. Applicants are, again, encouraged to submit data commensurate in scope with the claims to provide evidence that the claims are in fact enabled. As argued previously, the

invention is not an invitation to figure out which zwitterionic polymers work; the specification must demonstrate that the invention is enabled commensurate in scope with the claims.

Contrary to Applicant's assertion, the size of the genus of compounds encompassed does relate directly to the enablement requirement. The specification and/or state of the art must establish that that the genus of compounds may be used in the claimed invention as evidenced by a showing that a subset of the genus may be used and that the subset is representative of the genus as a whole. Otherwise, the claims directed to the genus as a whole are not enabled. The specification must set forth guidance and direction which can predictably be used to practice the claimed invention commensurate in scope with the claims. The Examiner stands behind the argument that the claims are directed to a nearly limitless genus. Applicant's argument regarding the fact that the charge motif is unique is not persuasive because the claims are not directed to anything natural. The claims encompass artificial polymers. As evidenced by the fact that Applicants have engineered peptides which have a repeating charge characteristic, all peptides of any length that have repeating negative and positive amino acids are encompassed by the instant claim recitation. The negative and positive amino acids need not be the same amino acid throughout the peptide, but only that the amino acids exhibit repeating negative and positive charges. In order to perform an enablement search on the genus of peptides encompassed by this claim recitation, the Examiner would need to identify every member of the genus of peptides having any length that are encompassed by the instant claim recitations. Then, she would need to send a sequence search out to determine if any matches have been used to treat any allergy. The same thing applies to polysaccharide polymers encompassed. Both natural and artificial polysaccharides may be modified and engineered to have the charge characteristic encompassed.

The genus of polysaccharide polymers may also comprise different free amino moieties and different negatively charged moieties and still be encompassed by the instant claim recitation. The specification does not demonstrate nor does the art teach that all members of this genus encompassed exhibit the same effects. The specification is not enabled for the genus of polymers encompassed by the instant claim recitation.

The term comprising is open language and it does encompass the addition of other molecules to the polymer. The "legal basis" is that claims are given their broadest reasonable definition. Applicant's assertion that "If the Examiner's argument were correct, no claim with the term "comprising" would be enabled because the claim could be interpreted to include additional components or steps that are required to obtain the claimed functionality" is unpersuasive. The Examiner is not examining any other claims. As applied to the instant claims, it is not enabled. The Examiner's interpretation of this claim language is consistent with the Patent Office's interpretation.

As the Examiner stated previously, claim 4 reads on prevention of allergy and the specification is not enabled for prevention of any allergic condition.

8. Claims 1-2, 4-7, 17-18 and 101 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of treating asthma in a mouse by injecting the mouse with isolated PSA1.

Applicant is not in possession of: a method for treating **an allergic condition other than asthma** in **a subject**, comprising: administering to **a subject** having an allergic condition other than asthma **an isolated polymer** in an effective amount to treat the allergic condition, wherein the polymer **comprises repeating units of a charge motif characteristic of B. fragilis polysaccharide A (PSA), the motif being a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxyl, phosphate, phosphonate, sulfate, and sulfonate** of claim 1; wherein the motif is a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of phosphate, phosphonate, sulfate, and sulfonate of claim 2; wherein the polymer is **a polysaccharide** of claim 5; wherein the polymer is **a bacterial capsular polysaccharide** of claim 6; wherein the polymer is PSA1 of claim 7; wherein the method further comprises administering to **the subject** an anti-allergy medicament selected from the group consisting of glucocorticoids, antihistamines, and anti-IgE antibodies of claim 17; wherein the administering comprises administering to **the subject** having **an allergic condition other than asthma** multiple doses of the **isolated polymer** to treat **the allergic condition** of claim18; and wherein the allergic condition other than asthma is urticaria of claim 101 for the same reasons as set forth in the Office Action mailed on 12/23/2008.

Applicant's arguments filed on 05/26/2009 have been fully considered, but are not found persuasive.

Applicant argues:

"The claimed invention pertains to a treatment of an allergic condition other than asthma or eczema by administration of a polymer with the recited charge motif. Applicant has shown that correlation exists between the structure of the recited polymers and the function of the claimed methods of treatment. Firstly, the specification provides a genus of well characterized polymers with a specific charge motif. Secondly, the specification shows that polymers as diverse as peptides and polysaccharides show an immunomodulatory effect, as long as they have the recited charge motif (See *e.g.,* Example 1, page 49 and Examples 6 and 7, pages 54-55). Thirdly, the methods of treatment are directed to allergic conditions, which is a single category disease that is well described in the art and is characterized by an increase in serum IgE in the subject. Fourthly, in Examples 5 and 8 of the specification (pages 52-57), Applicant shows that administration of the polymers with the recited charge motif result in a decrease in the level of IgE antibodies. Finally, the findings in the instant application are corroborated in the art, which has established the relationship between specific charge motif of the polymer and the immunomodulatory effect of the polymer. No more is required to show possession of the claimed invention.

According to the Examiner, the specification does not disclose a correlation structure of the polymer and function (ability to treat an allergic condition other than asthma) and in this case functional limitations (comprising repeating units of a charge motif characteristic of PSA) such that a skilled artisan would have known what polymers have the claimed function and functional limitations. The Examiner refers to *In re Kubin* and quotes "Without a correlation between structure and function, the claim does little more than define the claimed invention by function." Applicant respectfully disagrees with the assertion that the specification does not provide a correlation between structure and function. The specification provides what the structural requirements are for the polymers to have the claimed functionality. Namely, the polymer needs to have a structure comprising a repeating unit having a positively charged free amino moiety and a negatively charged moiety. In addition, Applicant shows that if this charge motif is modified, the polymer looses its immunomodulatory capacity. Thus, a correlation between structure and function is provided and the claimed invention can be distinguished over the scenario presented in the *In re Kubin* citation.

The Examiner states that "the art shows that not all polymers encompassed by the instant claim recitations are able to stimulate cellular immunity." Respectfully, Applicant does not believe that the Examiner has made such a showing. Applicant has demonstrated above, that the art cited by the Examiner, Mazmanian et al. and Kalka-Moll et al., support the methods of the claimed invention and do not support the assertion that the polymers encompassed by the claimed invention are not able to stimulate cellular immunity.

Further, according to the Examiner, the "specification must also set forth the structural features that allow one of ordinary skill in the art to produce the genus of polymers comprising repeating units of a charge motif characteristic of PSA" and that "the instant application identifies PSA1 and CP1 that have properties called for in the instant claims, but there is no guidance on other polymers with these properties." Respectfully, the specification provides how to produce the polymers with the recited charge motif and provides a multitude of examples. In addition, the specification shows that polymers as diverse as peptides and polysaccharides, with the specific charge motif show an immunomodulatory effect (See *e.g.,* Example 1, page 49 and Examples 6 and 7, pages 54-55). Furthermore, the specification has incorporated by reference US 5,679,654, US 5,700,787 and WO 00/59515. These documents provide a detailed analysis of polymers, including polysaccharides, with specific charge motifs and their immunomodulatory effects. The teachings in these documents show that polymers with the motif recited in the instant application have a predictable and consistent immunomodulatory effect, while polymers with a slightly different

charge motif do not have such an effect (See *e.g.,* WO 00/59515, pages 35-43). Thus, the speciation provides a representative number of species of the claimed genus.

According to the Examiner, "the term "comprising" is open language that opens the claimed polymers to include additional molecules wherein the methods are not the result of the charge motif of the polymers at all". Respectfully, as demonstrated under the enablement rejection, Applicant maintains that the Examiner' s interpretation of claims reciting the connector "comprising" has no legal basis.

Thus, Applicant has provided a representative number of species for the claimed genus, and Applicant has shown that correlation exists between the structure of the recited polymers and the function of the claimed methods of treatment. Based on the teachings in the specification, a person of ordinary skill in the art would understand that Applicant had possession of the claimed invention at the time of filing of the application. In addition, Applicant believes that the Examiner has not shown that Applicant did not have possession of the claimed invention at the time of filing.."

It remains the Examiner's position that the specification does not disclose a correlation structure of the polymer and function (ability to treat an allergic condition other than asthma) and in this case functional limitations (comprising repeating units of a charge motif characteristic of B fragilis polysaccharide A (PSA), the motif being a positivley charged free amino moiety and a negatively charged moiety selected from the group consiting of carboxyl, phosphate, phosphonate, sulfate and sulfonate) such that a skilled artisan would have known what polymers have the claimed function and functional limitations. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" In re Kubin, of record, at page 16. In this instant case, Applicants have not provided any guidance as to what polymers will result in the claimed functions and functional limitations. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17.

It is the Examiner's position that, contrary to Applicant's assertion the genus of all "polymers" that exhibit the "charge motif of B. fragilis polysaccharide A (PSA) the motif being a positively charged free amino moiety and a negatively charged moiety selected from the group consisting of carboxyl, phosphate, phosphonate, sulfate, and sulfonate" is not well-characterized at all. As the Examiner has stressed previously, the claims read on any molecule with that charge motif. Some compounds of this genus are well-characterized. However, the number of compounds which are characterized are not representative of the genus of compounds encompassed. It is an undue burden to determine the genus of polymers encompassed by such a claim recitation.

The specification has not shown that a single polymer has the claimed functionality, much less the genus of polymers encompassed. The specification has not treated any allergic condition other than asthma with any polymer, nor has the specification treated more than one allergic condition other than asthma with any single polymer. Therefore, the specification has certainly not shown that every polymer can treat every allergic condition other than asthma.

Allergic conditions are not "a single category of disease" that may be treated by the same method, the Examiner provides a number of references that teach this fact. Kormelink et al. (PTO-892; Reference U) teaches that there is a subgroup of allergic diseases that displays common symptoms of allergies associated with IgE and have activated mast cells, but lack elevated levels of total serum IgE and antigen specific IgE. In patients with non-IgE related allergic disorders, therapies that target IgE will not work (In particular, abstract). Kormelink et al. also teaches that this set of allergic disorders may be mediated by free immunoglobuilin light chains (In particular, abstract, whole document). Jyonouchi et al. (PTO-892; Reference V)

teaches that non-IgE mediated food allergies primarily affect the gastrointestinal mucosa and display their own unique immune reactivity and cytokine production profile, which differs from that of IgE mediated food allergy and is typically only treated with an elimination diet. (In particular, abstract, pages 5-6, whole document). Greenberger et al. (PTO-892; Reference W) teaches that drug allergy is unpredictable and may be IgE mediated or non-IgE mediated (In particular, abstract). Bilo et al. (PTO-892; Reference X) teaches that Hymenoptera venom allergy may be IgE-mediated or non-IgE mediated (In particular, abstract, paragraph spanning page 1341-1342, first full paragraph on page 1345, whole document). Boguniewicz et al. (PTO-892; Page 2; Reference U) and Poonawalla et al. (PTO-892; Page 2; Reference V) teaches that urticaria, a skin rash, is caused by a number of autoimmune and other diseases, drugs, allergens, mechanical and thermal effects and sun damage (In particular Boguniewicz: Tables I and II, whole document; Poonawalla: Table I, whole document). Therefore, the terms "allergic condition," "urticaria" and "food allergy" are not single categories of disease mediated by IgE, contrary to Applicant's assertion. Therefore, the claimed method of treating all allergic conditions other than asthma is not enabled by the specification. In addition, the specification, which teaches treating asthma by the instant method is not enabling because Lemanske et al. (PTO-892; Page 2; Reference W) teaches that asthma is a complex disease having both genetic and environmental factors which, as of 2009, is not curable and whose treatment is complicated and mostly aimed at just controlling symptoms (In particular, abstract, whole document). The animal model of asthma provided in the specification is not substantiating evidence in the form of animal tests which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences

1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746.

It is the Examiner's position that Tzianabos et al. teaches that in vitro and in vivo T cell activation using peptides with a zwitterionic charge motif depends on the number of repeating units. Zwitterionic peptides with less than 15 repeating untits were unable to stimulate T cells in vitro or in vivo. Therefore, the effects of the polymers encompassed, particularly with respect to peptides, are limited by size. Further, Kalka-Moll (IDS; 06/21/2004) teaches that polymer length affects the ability to stimulate cellular immunity, so zwitterionic polymers having different structures stimulate cellular immunity differently. Polymers of different lengths have different structures. Since all zwitterionic polymers of Kalka-Moll et al. are encompassed by the instant claim recitations, the reference shows that different zwitterionic polymers have different cell stimulatory effects and would in turn have different in vivo effects. The post-dated state of the art of Mazmanian et al. (PTO-892 mailed on 12/23/2008; Reference U) teaches that the recited zwitterionic polymers interact with T cells, B-cells and can direct the development of the immune-system toward a Th1 phenotype to suppress inflammation in general. However, the reference does not teach or suggest that zwitterionic polymers may be used to treat any particular allergy, much less all allergies or that zwitterionic polymers have any direct or indirect affect on IgE production. Applicants are, again, encouraged to submit data commensurate in scope with the claims to provide evidence that the claims are in fact enabled. As argued previously, the invention is not an invitation to figure out which zwitterionic polymers work; the specification must demonstrate that the invention is enabled commensurate in scope with the claims.

Contrary to Applicant's assertion, the size of the genus of compounds encompassed does relate directly to the written description requirement. The specification must establish that that

the genus of compounds may be used in the claimed invention as evidenced by a showing that a subset of the genus may be used and that the subset is representative of the genus as a whole. Otherwise, the claims directed to the genus as a whole are not described. The Examiner stands behind the argument that the claims are directed to a nearly limitless genus. Applicant's argument regarding the fact that the charge motif is unique is not persuasive because the claims are not directed to anything natural. The claims encompass artificial polymers. As evidenced by the fact that Applicants have engineered peptides which have a repeating charge characteristic, all peptides of any length that have repeating negative and positive amino acids are encompassed by the instant claim recitation. The negative and positive amino acids need not be the same amino acid throughout the peptide, but only that the amino acids exhibit repeating negative and positive charges. The specification does not described that all members of this genus encompassed exhibit the same effects. The specification is has not described the genus of polymers encompassed by the instant claim recitation.

The term comprising is open language and it does encompass the addition of other molecules to the polymer. The "legal basis" is that claims are given their broadest reasonable definition. The Examiner's interpretation of this claim language is consistent with the Patent Office's interpretation.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-2, 4-7 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/59515 (IDS filed on 06/21/2004) in view of Tang et al. (PTO-892 mailed 05/18/2007, Page 2, Reference U) for the same reasons as set forth in the Office Action mailed on 12/23/2008.

Applicant's arguments filed on 05/26/2009 have been fully considered, but are not found persuasive.

Applicant argues:

" The combination of the teachings of WO/59515 and Tang et al. does not render obvious the treatment of allergic disorders by administering polymers with the recited charge motif.

Applicant maintains that WO 00/59515 does not teach "switching the immune response from a Th2 response to a Thl response by the administration of the recited polysaccharides". WO 00/59515 merely teaches that the administration of the recited polysaccharides results in the induction of a Thl profile. The attempts by the Examiner to equate a switch from a Th2 response to a Thl response with the induction of a Thl response are unfounded based on the cited references and the art in general.

The Examiner states on page 16 of the Office Action that "one of ordinary skill in the art *knows* that Thl responsive disorders are those that "respond" by making the Th cytokine profile Thl. If the disorder "responds" by making it Thl, then it is not currently Th1. Therefore, it must necessarily be Th2". Respectfully, Applicant disagrees with this reasoning. Firstly, the Examiner's argument is based on what one of skilled in the art allegedly *knows* without providing support for this assertion. Secondly, a disorder that does not results in the induction of a Thl cytokine profile, is merely a disorder that does not result in the induction of a Thl response. A disorder that fails to respond with a Thl cytokine profile does not make the disorder a Th2 disorder. For instance, as shown by Tang et al., dendritic cells are responsible for the induction of a Th2, while antigen- presenting macrophages are responsible for the induction of Thl. While the induction of antigen- presenting macrophages would result in the induction of a Thl response, the induction of a Thl response does not automatically mean that a Th2 response is not induced, as this would rely on the induction of different cells. Thus, the induction of Thl and Th2 responses are not necessarily correlated and the induction of a Thl response does not necessarily imply a switch from Th2 to Thl.

The Examiner further supports the assertion that WO 00/59515 teaches switching the immune response from a Th2 response to a Thl response by referring to the post-filing teachings of Mazmanian et al. Applicant respectfully disagrees with this reasoning. Mazmanian et al. is a post- filing teaching co-

> authored by an inventor of the instant application. Thus, Mazmanian et al. cannot be used to support the argument that the instant application was obvious.
>
> Thus, at least for the reasons presented above, the combination of WO00/59515 and Tang et al. does not render obvious the methods of the rejected claims."

WO 00/59515 teaches treating Th1 responsive disorders with the same recited polymer. Column 23, line 60 to column 24, line 7 teaches driving the immune response toward a Th1 response when it is desirable to have a Th1 cytokine response to treat disease, as is the case for allergies. Tang et al. teaches that allergic inflammation is a Th2-mediated disease, an immune switch to Thl can protect against Th2-mediated allergic responses and that Thl stimulating activity of lung macrophages is responsible for the inhibition of allergic airway inflammation. It is obvious to use a polymer to drive the cytokine profile to that of Th1 to treat allergies, which are generally mediated by a Th2 cytokine profile and which are treated by a switch to Th1 cytokine responses.

The post-dated art of Mazmanian et al. (PTO-892 mailed on 12/23/2008; Reference U) can be used as an evidentiary referent to show that the Examiner has not misinterpreted the teaching of a reference. Mazmanian et al. is not being used in the rejection but rather is being used to support the Examiner's assertion of obviousness in that the reference teaches that the zwitterionic polymers of the instant claims affect the formation of allergy by driving a Th1 response (In particular, page 854, right column to page 857, Box 2, whole document).

Although Applicant acknowledges that WO00/59515 teaches the isolated polymers can be used to treat Thl responsive disorders and that when T cells are stimulated, they differentiate toward either Th1 or Th2 cytokine production, Applicant's argues that WO00/59515 does not

teach switching the immune response from a Th2 response to a Thl response. The Examiner remains unpersuaded by this argument. Tang et al. teaches that allergic inflammation is a Th2-mediated disease, an immune switch to Thl can protect against Th2-mediated allergic responses and that Thl stimulating activity of lung macrophages is responsible for the inhibition of allergic airway inflammation. So, unless one would be unable interpret a Th1 responsive disorder as being one that specifically does not include switching the immune response from a Th2 response to a Thl response, then the art applies. Since there is no such teaching in WO00/59515, the rejection stands.

11. Claims 1-2, 4-7 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,026,285 (PTO-892, Reference B) in view of Tang et al. (PTO-892 mailed 05/18/2007, Page 2, Reference U) for the same reasons as set forth in the Office Action mailed on 12/23/2008.

Applicant's arguments filed on 05/26/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> " Claims 1-7 and 18 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent 7,026,285 in view of Tang et al. *(supra).* Applicant respectfully requests reconsideration. The cited patent is the U.S. equivalent of WO 00/59515. The rejection should be withdrawn for the same reasons as discussed above in connection with WO 00/59515.
>
> Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1-7 and 18 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,026,285 in view of Tang et al.
>
> ."

It is the Examiner's position that the rejection of Claims 1-2, 4-7 and 18 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 7,026,285 (PTO-892, Reference B) in view of Tang et al. (PTO-892, Page 2, Reference Y) is maintained for the same reasons as set forth *supra* with regard to WO 00/59515 and Tang et al.

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 29, 2009
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/Maher M. Haddad/
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